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Original research

Pancreaticojejunostomy by reinforcing the pancreas without covering the anastomotic line reduces pancreatic fistula

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ABSTRACT

Background/objective: Postoperative pancreatic fistula (POPF) is the most common and an intractable complication after pancreaticoduodenectomy (PD). Many efforts have been made to lessen POPF, but nevertheless its incidence still remains high. The aim of this study was to evaluate the efficacy of reinforcing the pancreatic remnant, but the non-reinforcement of the anastomotic line, by using a modified polyethylene glycolic acid (PGA) felt pasting method after PD, especially in cases with a soft pancreas.

Methods: Pancreaticojejunostomy (PJ) anastomosis was performed with the end-to-side 2-layer manner in which the cut end of the pancreatic remnant was pasted with PGA felts using a fibrin sealant in 31 patients (PGA group). The postoperative outcome was then compared with historical control subjects (control group, 33 patients).

Results: Incidences of overall, Grade A and Grade B of POPF in the PGA group were 29.0, 22.6 and 6.5%, respectively, and tended to be lower than that in the control group (48.5, 33.3 and 15.2%), although no statistical significance was observed. There was no Grade C of POPF in this study. Referring only to the soft pancreas, however, the overall incidence of POPF in the PGA group was significantly lower than that in the control group (39.1 vs. 70.0%, $p = 0.042$).

Conclusion: Applying PGA felt pasting to PJ anastomosis could be one effective measure for reducing POPF after PD.

1. Introduction

Pancreaticoduodenectomy (PD) has been done increasingly in recent years for patients with malignant and benign lesions of the pancreas and periampullary areas. Although significant advances in the surgical techniques and perioperative management have dramatically reduced the mortality associated with pancreatic surgery, the postoperative morbidity after PD still remains considerably high at 40–50%.[1–3] One major complication following pancreatic resection is leakage from the pancreaticoenteric anastomosis or postoperative pancreatic fistula (POPF). POPF is the main trigger for other morbidities such as intra-abdominal abscess, sepsis, and bleeding, which are closely associated with the high mortality rates.[4–8] The incidence of POPF has been reported to range from 10% to 40% in patients after PD,[9–12] but there is still no consensus on the best way of managing the pancreaticoenteric anastomosis.

The two most common factors for the leakage of pancreatic anastomosis are considered to be the soft texture in the pancreas and a small-sized pancreatic duct, and controlling the pancreaticoenteric anastomosis in patients with such high-risk glands is considered to be of utmost importance. Many surgeons attempt to minimize POPF by applying various surgical techniques, but the ensuing results have been mostly unsuccessful in alleviating the problem.[9–12]

Fibrin sealant is being widely utilized as a valuable product to prevent POPF in patients who undergo pancreatic surgery.[13,14] However; there is the risk that this adhesive might not sufficiently block every opening in the small branches of the pancreatic ducts by itself alone. Polyethylene glycolic acid (PGA) felt is an absorbable sheet, and has been frequently used accompanied by

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fibrin sealant in thoracic surgery. A newly devised method of using this PGA felt in conjunction with fibrin sealant in pancreaticojejunal (PJ) anastomosis has been reported to be a useful strategy, and has yielded favorable data on the reduction of POPF.[15,16] But, on the other hand, there are reports which claim that there are no benefits in using PGA felts with fibrin glue sealant in PJ anastomosis.[17] We hypothesized that the covering of the PJ anastomotic line itself is probably one reason for the disappointing outcomes, that is, by doing so interrupts the drainage of the exudate from a cut end of the pancreas, which then leads to the creation of liquid collections causing infections that eventually lead to POPF.

Therefore, we recently devised a modified PGA felt pasting method for PJ anastomosis. Our concept is 'not reinforcing PJ anastomosis but reinforcing the pancreatic remnant'. What this entails is making a strong artificial membrane by using the PGA felt in conjunction with fibrin sealant to enable the creation of a firm PJ anastomosis without tearing the pancreas parenchyma. In this study, we tried to evaluate the efficacy of applying the PGA felt pasting method to PJ anastomosis for the reduction of pancreatic fistula after PD, especially in patients with a soft pancreas.

2. Patients and methods

2.1. Patients

Between April 2007 and April 2013, 64 consecutive patients who underwent pancreatic head resection at Kumamoto Social Insurance General Hospital were included in this study. Between April 2007 and February 2010, 33 patients received no adjuvant surgical technique for PJ anastomosis (control group), while the remaining 31 patients had the PGA felt pasting method between April 2010 and April 2013 (PGA group).

2.2. Surgical technique

After the completion of the resection, preparation of the remnant pancreas for reconstruction was performed. The bleeding from the cut surface of the parenchyma was closely coagulated by electrocautery, and approximately 1.5–2.0 cm of the cut end of the pancreatic remnant was mobilized from the surrounding tissues. In the PGA group, first, PGA felts were prepared as pieces cut in sizes of 1.5–2.0 × 4.0–5.0 cm. Then, the cut end of a pancreatic remnant which was to be the suture site for PJ anastomosis was pasted around with a couple of pieces of PGA felt by using fibrin glue sealant (the cut surface was not pasted), which would play the role of a pledget in suturing the pancreas parenchyma. The reconstruction was performed by a modified Child's procedure (exclude 3 cases of pyrolus preserving PD) and PJ anastomosis was performed with the end-to-side 2-layer anastomosis in all of the patients. In the PGA group, the pancreatic parenchyma was sutured penetratingly with six to eight stitches of 4-0 resolvable monofilament threads (PDS-2; Ethicon, Japan) through the PGA felt and seromuscular layer of the jejunum. Those threads were held under tension during the anastomosis of the inner layer. Anastomosis between a pancreatic duct and jejunal wall was performed by eight interrupted sutures with 5-0 PDS-2 and a pancreatic duct tube was placed as an external drainage stent. Then the threads which had been held under tension were tied, and the PJ anastomosis was completed (Fig. 1). In the control group, the same procedure was adopted except for the use of the PGA felts and fibrin sealant. Subsequently, the biliary-jejunal and gastro-jejunal anastomoses were performed and drains were routinely placed closely to the PJ anastomosis. All operations were performed by two experienced surgeons with more than 15 years of a surgical career.

Perioperative management was standardized. All the patients received antibiotic prophylaxis (Cefazolin 1 g) intravenously at the beginning of the operation. Antibiotic therapy was repeated every 4 h during the operation. And also all patients routinely received proton pomp inhibitor during their postoperative hospitalization as prophylaxis for stress and marginal ulceration. Postoperative octreotide was not given to any of the patients.

2.3. Data recording

The intraoperative variables included operation time, blood loss, blood transfusion (with or without), texture of the pancreas gland and pancreatic duct size (≤3 mm, >3 mm). The texture of the pancreas was classified as soft or hard by the operating surgeon's discretion and the pancreatic duct size was actually measured at the cut surface of the remnant pancreas.

Postoperative variables included measurement of the amylase concentration in serum and drainage fluid on postoperative days 1, 3, 5 and 7. POPF was defined and graded according to the criteria recently proposed by the International Study Group on Pancreatic Fistula (ISGPF).[18] POPF is defined as a drain out-put of any measurable volume of fluid on or after postoperative day 3 with amylase content greater than 3 times the serum amylase activity. Severity of POPF was set according to its clinical impact into three

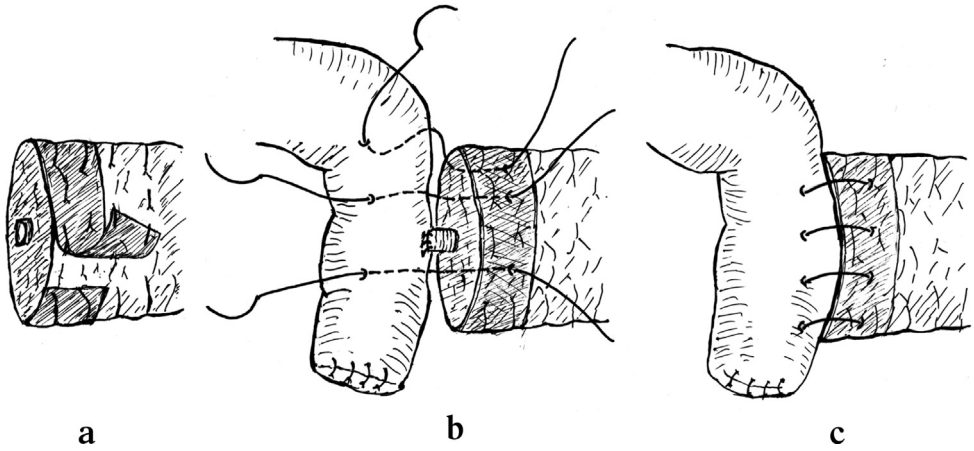

Fig. 1. Schema of the polyethylene glycolic acid (PGA) felt pasting method. a. Paste a couple of PGA felts (1.5–2.0 × 4.0–5.0 cm in size) with fibrin sealant around the cut end of the pancreatic remnant. b. End-to-side 2-layer anastomosis is performed. Suture the cut end of the pancreas remnant reinforced with PGA felts and seromuscular layer of jejunum. C. Completion. The line of anastomosis is not covered with the PGA felts.

grades: A (no clinical impact), B (minor adjustment on the clinical pathway), and C (major change in the clinical management). A computed tomography scan was performed on postoperative day 7, and the peripancreatic drains were removed when there was no abnormal finding. The pancreatic duct tube was removed at our outpatient clinic around 4 weeks after the operation.

2.4. Statistical analysis

Categorical variables were compared using the Chi-squared test or Fisher's exact test, and continuous variables were compared using the Student's *t*-test. A p value of <0.05 was considered as statistically significant.

3. Results

The clinicopathological characteristics for each group were compared as shown in Table 1. There were 27 men and 37 women with a mean age of 65.3 (range: 38–82) years. The pathological conditions included pancreatic cancer ($n = 15$), bile duct cancer ($n = 23$), ampullary cancer ($n = 16$), intraductal papillary mucinous neoplasms ($n = 4$), duodenal cancer ($n = 4$) and others ($n = 2$). For all the patients with jaundice, preoperative biliary drainage was performed endoscopically or percutaneously. There was no statistically significant difference in the clinicopathological factors between the two groups.

Parameters related to operations are shown in Table 2. Pancreatic head resections were achieved by subtotal stomach preserving pancreaticoduodenactomy (SSPPD; $n = 56$), pylorus preserving pancreaticoduodenectomy (PPPD; $n = 3$) and standard PD (PD; $n = 5$). There was no statistical difference between the two groups as to type of PD, operation time, blood loss, amount of transfusion, pancreatic duct size and texture.

Table 3 shows postoperative outcomes and complications. Overall incidences of POPF in the PGA group and control group were 29.0% and 48.5%, respectively. The incidence of POPF in the PGA group was lower than that in the control group although there was no significant difference between the two groups ($p = 0.090$). Grade A and B of POPF in the PGA group and control group were 22.6%, 6.5% and 33.3%, 15.2%, respectively. Grade A and B of POPF in the PGA group also tended to be lower than that in the control group, but no significant observation was evident. There was no Grade C of POPF in this study. No significant differences were found in incidences of abdominal abscess, delayed gastric emptying or the other complications between these two groups.

Incidences of POPF in patients with a soft texture of the pancreas were examined (Table 4). Overall incidence of POPF in the PGA group was significantly lower than that in control group (39.1% vs. 70.0%, $p = 0.042$). There was no significant difference in the incidence of POPF Grade A and B between the two groups.

Table 1
Clinicopathological characteristics of enrolled patients.

	PGA	Control	*p*-Value
	$n = 31$	$n = 33$	
Age (mean ± SD)	63.1 ± 9.1	67.4 ± 7.5	0.87
Male/female	18/13	9/24	0.26
Diagnosis			
Pancreatic cancer	6 (19.4)	9 (27.3)	0.54
Bile duct cancer	14 (45.2)	9 (27.3)	0.55
Ampullary cancer	7 (22.6)	9 (27.3)	0.74
IPMT of pancreas	1 (3.2)	3 (9.1)	0.68
Duodenal cancer	2 (6.5)	2 (6.1)	0.72
Others	1 (3.2)	1 (3.0)	0.89
BMI (kg/m^2 ± SD)	22.0 ± 4.3	21.8 ± 5.6	0.84
Preoperative biliary drainage (±)	14/31(45.2)	15/33(45.5)	0.78

Items in parentheses are percentages.
PGA, polyethylene glycolic acid; IPMT, intraductal papillary-mucinous tumor; BMI, body mass index.

Table 2
Parameters related to operations.

	PGA	Control	*p*-Value
	$n = 31$	$n = 33$	
Operation method			
SSPPD	29 (93.5)	27 (81.8)	0.71
PPPD	1 (3.2)	2 (6.1)	0.85
PD	1 (3.2)	4 (12.1)	0.29
Operation time (min)	351	392	0.89
Blood loss (ml)	858	718	0.26
Transfusion (+)	7 (22.6)	8 (24.2)	0.75
Pancreas texture (soft/hard)	23/8	20/13	0.56
Diameter of pancreatic duct (3 mm<)	7 (22.6)	10 (30.3)	0.76

Items in parentheses are percentages.
PGA, polyethylene glycolic acid.
SSPPD, subtotal stomach preserving pancreatoduodenectomy.
PPPD, pylorus preserving pancreatoduodenectomy; PD, pancreatoduodenectomy.

4. Discussion

POPF is a major cause of subsequent morbidity and it is associated with other significant complications, including intra-abdominal abscess, intra-abdominal hemorrhage and sepsis, and is often linked with a high mortality rate. The incidence of POPF reported in the surgical literature still remains high although many surgeons have made diligent efforts to prevent POPF after PD.[19,20] Through the numerous attempts to reduce the incidence of POPF, several risk factors have been identified, out of which the risk factors related to the pancreas, such as the pancreatic texture and pancreatic duct size, have been considered the most significant. The soft texture of the pancreas and the narrow pancreatic duct are widely regarded as high risk factors and these two risks are mostly concomitant.[21] It is generally accepted that a fibrotic pancreatic remnant facilitates the healing of the pancreatic anastomosis, whereas a soft pancreatic remnant makes the anastomosis difficult to perform.[19] Actually, in this study, we had no case of POPF in the patients having a hard pancreas. These findings correlate well with others which previously reported the low incidence of POPF in a hard pancreas.

Various measures for reducing the incidence of POPF have been tested, including technical alterations (e.g. modification of the pancreaticojejunostomy, reconstruction with a pancreaticogastrostomy and the placing of a pancreatic duct stent), the

Table 3
Comparison of incidences of postoperative complications.

	PGA	Control	*p*-Value
	$n = 31$	$n = 33$	
POPF			
Overall	29.0 (9)	48.5 (16)	0.090
Grade A	22.6 (7)	33.3 (11)	0.249
Grade B	6.5 (2)	15.2 (5)	0.240
Grade C	0	0	–
Abdominal abscess	6.5 (2)	3 (1)	0.283
DGE	6.5 (2)	9.1 (3)	0.530
Others	3.2 (1)	3 (1)	0.769

Values are percentages, Items in parentheses are numbers of patients.
PGA, polyethylene glycolic acid.
POPF, postoperative pancreatic fistula.
DGE, delayed gastric emptying.

Table 4
Comparison of POPF in the patients with soft texture of pancreas.

	PGA	Control	*p*-Value
	$n = 23$	$n = 20$	
Overall	39.1 (9)	70.0 (14)	0.042[a]
Grade			
A	30.4 (7)	45.0 (9)	0.252
B	8.7 (2)	25.0 (5)	0.152
C	0	0	–

Values are percentages, items in parentheses are numbers of patients.
PGA, polyethylene glycolic acid.
[a] Statistically significance.

perioperative administration of somatostatin analogues and the use of adhesive sealants.

Fibrin sealant is generally used to prevent the leakage of gastrointestinal anastomoses and hemorrhages in parenchymal organs, and has been also reported to be effective for the reduction of POPF in pancreatic surgery.[22–24] Although some studies have suggested that fibrin sealant can decrease the incidence of POPF, others have found no additional benefit in adopting this approach.[25–27] Fibrin sealant may be able to block minor leakages of exocrine pancreatic secretion from the small branches of the pancreatic duct, but its effectiveness for the complete prevention of POPF may not be sufficient.[26] This is especially a possibility in cases with serious pancreatic high-risks glands, when the high capacity of pancreatic juice output could increase the risk of POPF, and, moreover, the apparent softness and weakness of the pancreas texture are supposed to make the tight fixation of the pancreas and intestine highly difficult.

Employing the technique of applying a PGA felt in conjunction with fibrin sealant to PJ anastomosis is one of the new attractive methods that are expected to decrease the incidence of POPF. Although the combined use of PGA felt and fibrin sealant is common in thoracic surgery to prevent air leakage from the lung,[28] only a few reports on the application of this surgical combination method to pancreatic surgery have appeared. Ochiai et al. have demonstrated that the procedure of using a PGA felt with fibrin sealant significantly reduced the incidence of severe POPF after pancreatic surgeries and also that this procedure was a significant independent factor in the prevention of severe POPF.[15] On the other hand, however, Satoi et al. have claimed that the reinforcement of PJ anastomosis using PGA felts and fibrin sealant provided no significant benefit in reducing the frequency of POPF.[17]

One reason for the discrepancy of opinion regarding the application of the PGA felts and fibrin sealant to PJ anastomosis could lie in the myriad variations of pasting and placing of the PGA felts. Our supposition is that the complete wrapping and sealing up of the PJ anastomosis could cause certain conditions where the exudate, including the pancreatic juice from the small ductal branches of the cut surface of the pancreatic remnant, is collected and that this development, in turn, leads to PJ anastomosis infection and finally ends up in POPF. Such exudates do not seem to include very high concentrations of pancreatic juice and should, in our opinion, be immediately drained out.

Based on our reasoning, we clearly defined the role of the PGA felt. We concluded that the PGA felt should be used not to tightly seal the PJ anastomosis in order to block the liquid oozing from the cut end of the pancreas but solely to reinforce the surface of the pancreatic remnant for a tight fixation to the jejunum. Thus, we did not actually cover the PJ anastomosis with the PGA felts, which apparently is the crucial difference from that of other methods of applying the PGA felts and fibrin sealant as previously demonstrated. In this study, we used the PGA felt as a pledget to prevent the pancreatic tissue from being ruptured by suturing. We surmised that the PGA felt might work not merely as a cushion for the thread knots but also as an artificial tough serosa of the pancreas itself, which would enable us to create a firm PJ anastomosis, and that it should allow us to suture and fasten the threads much more easily and steadily without tearing the pancreas itself.

In this study, we obtained favorable results with this new technique for the reduction of POPF in the patients with high-risk glands of pancreas. Our results demonstrated that the PGA felt pasting method significantly decreased the incidence of POPF in patients with soft pancreas; POPF was observed in 39.1% of the patients in the PGA group and in 70.0% of patients in the control group, and surprisingly, we had only 2 patients of Grade B (8.7%). As for Grade C, we had none in this study. We had two cases of an abdominal abscess in the PGA group, but neither case was connected with PJ anastomosis: one was an abscess around the feeding tube projecting out through the jejunum, and the other case was due to the partial necrosis of an omentum.

Although recently many surgeons have come to adopt the criteria of ISGPF for the evaluation of POPF, their clinical validity still remain quite controversial.[29–31] Kim et al. have demonstrated that only Grade B and C fistulae should be considered POPF in practice, because no difference was evident between the patients without a fistula and Grade A in terms of clinical findings.[29] Based on this point of view, it is plausible that the very low incidence of Grade B and C POPF evident in our data is both significant and attractive.

In conclusion, we would like to suggest that applying the PGA felt in conjunction with fibrin sealant to PJ anastomosis could be one effective measure for reducing POPF. However, further detailed clinical studies, including randomized controlled trials, need to be conducted for the objective evaluation and final validation of this method.

Ethical approval

We obtained written consents from all the patients.

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Author contribution

Masafumi Kuramoto: main author, study design, data analysis, writing.

Satoshi Ikeshima, Kenichiro Yamamoto, Toshiro Masuda, Kenichi Nakamura: data collections.

Shinya Shimada, Toichiro Takeguchi, Hideo Baba: study design.

Conflicts of interest

We attest that all authors have no conflicts of interest.

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